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*Attorneys for Defendant Celgene Corporation*

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**

| | |
|---|---|
| HUMANA INC.,<br><br>Plaintiff,<br><br>v.<br><br>CELGENE CORPORATION,<br><br>Defendant. | Civil No. 2:19-CV-07532-ES-MAH<br>Hon. Esther Salas, U.S.D.J.<br>Hon. Michael A. Hammer, U.S.M.J.<br><br>**DECLARATION OF BENJAMIN M. GREENBLUM ATTACHING EXHIBITS**<br><br>**DOCUMENT FILED ELECTRONICALLY** |

I, **BENJAMIN M. GREENBLUM**, declare as follows:

1. I am a partner at Williams & Connolly, LLP, counsel to Defendant Celgene Corporation ("Celgene"), and an attorney of record in this matter.

2. I submit this declaration in support of Celgene's Memorandum of Law in Support of its Motion to Dismiss Humana Inc.'s Complaint.

3. I have personal knowledge to state the following facts.

4. Exhibit 1 is a true and correct copy of the Decision Denying Institution of *Inter Partes Review, Coalition for Affordable Drugs VI, LLC v. Celgene Corp.*, No. IPR2015-01169 (P.T.A.B. Nov. 16, 2015).

5. Exhibit 2 is a true and correct copy of Dr. Reddy's Laboratories, Inc.'s Citizen Petition filed with the United States Food and Drug Administration on June 10, 2009, downloaded from https://www.regulations.gov/document?D=FDA-2009-P-0266-0001.

6. Exhibit 3 is a true and correct copy of excerpts from Celgene's 2009 Form 10-K filed with the United States Securities and Exchange Commission.

7. Exhibit 4 is a true and correct copy of excerpts from Celgene's 2010 Form 10-K filed with the United States Securities and Exchange Commission.

I hereby certify that the foregoing statements made by me are true. I am aware that if the foregoing statements made by me are willfully false, I am subject to punishment.

BENJAMIN M. GREENBLUM

Date: May 22, 2019

# EXHIBIT 1

Trials@uspto.gov
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Paper 22
Entered: November 16, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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COALITION FOR AFFORDABLE DRUGS VI LLC,
Petitioner,

v.

CELGENE CORPORATION,
Patent Owner.

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Case IPR2015-01169
Patent 5,635,517

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Before TONI R. SCHEINER, JACQUELINE WRIGHT BONILLA, and TINA E. HULSE, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
*37 C.F.R. § 42.108*

# I. INTRODUCTION

Coalition For Affordable Drugs VI LLC ("Petitioner" or "CFAD") filed a Petition requesting *inter partes* review of claims 1–10 of U.S. Patent No. 5,635,517 (Ex. 1001, "the '517 Patent"). Paper 1 ("Pet."). Celgene Corporation ("Patent Owner") filed a Preliminary Response. Paper 16 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any claim challenged in the Petition. Accordingly, we decline to institute an *inter partes* review.

## *A. Related Proceedings*

The parties indicate that the '517 patent is the subject of a district court proceeding, *Celgene Corporation v. Natco Pharma Ltd.*, C.A. No. 2:10-cv-5197 (D.N.J.) (including consolidated related C.A. No. 2:12-cv-4571 (D.N.J.)). Pet. 8; Paper 7. On October 27, 2015, the Board instituted *inter partes* reviews of challenged claims in two unrelated patents owned by Patent Owner, challenged by Petitioner, in Case Nos. IPR2015-01092 (Paper 20), IPR2015-01096 (Paper 21), IPR2015-01102 (Paper 21), and IPR2015-01103 (Paper 22).

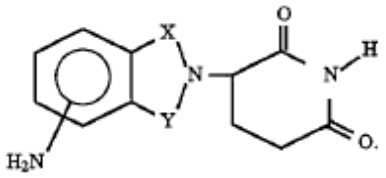
## *B. The '517 Patent*

The '517 patent is directed to methods of reducing levels of tumor necrosis factor α ("TNFα") in a mammal by administering "amino

substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines and 1,3-dioxoisoindolines," i.e., certain thalidomide analogs with an added amino group (-$NH_2$) in a benzene ring of the chemical structure. Ex. 1001, 1:6–11; *see also* Pet. 1, 15–16 (showing chemical structures of thalidomide and compounds recited in claims 3–10).

The '517 patent discloses that TNFα is a cytokine released by mononuclear phagocytes in response to immunostimulators. Ex. 1001, 1:14–16. Excessive or unregulated TNFα production has been implicated in a number of diseases. *Id*. at 1:21–3:18. "Decreasing TNFα levels and/or increasing cAMP levels" may help treat "many inflammatory, infectious, immunological or malignant diseases." *Id*. at 3:59–4:6.

The '517 patent describes the discovery that certain compounds "decrease the levels of TNFα and elevate the levels of adenosine 3',5'-cyclic monophosphate" ("cAMP"), and that such compounds have the formula:




I

in which one of X and Y is C═O and the other of X and Y is C═O or $CH_2$

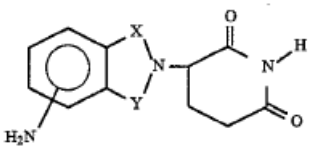
*Id*. at 4:20–33. Thus, the disclosed compounds have an amino group (-$NH_2$) group attached to a carbon in the left 6-carbon benzene ring portion and, in some compounds, X is a C=O and Y is a $CH_2$ in the 5-carbon ring portion.

*C. Illustrative Claims*

The '517 patent contains ten claims. Independent claims 1 and 10 and dependent claims 2 and 7 are representative, and are reproduced below.

> 1. The method of reducing undesirable levels of TNFα in a mammal which comprises administering thereto an effective

amount of a compound of the formula:



in which in said compound one of X and Y is C=O and the other of X and Y is C=O or $CH_2$.

2. The method according to claim 1 in which X is C=O and Y is $CH_2$.

7. The method according to claim 1 in which each of X and Y is C=O.

10. A compound selected from the group consisting of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline, 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, 1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline, and 1-oxo-2-(2,6-dioxopiperidin-3-yl)-7-aminoisoindoline.

Dependent claims 3–6 depend from claim 2, and claims 8 and 9 depend from claim 7.

*D. Proposed Grounds of Unpatentability*

Petitioner advances three grounds of unpatentability under 35 U.S.C. § 103 in relation to the challenged claims in the '517 patent (Pet. 11):

| **References** | **Statutory Basis** | **Challenged Claims** |
|---|---|---|
| Piper (Ex. 1002)[1] in view of Kaplan (Ex. 1003)[2] | § 103 | 1, 7–9 |

[1] Piper et al., *Anti-inflammatory immunosuppressive thalidomide analogs*, 49(4) INT'L J. OF LEPROSY 511–512 (1981) ("Piper") (Ex. 1002)
[2] Kaplan et al., U.S. Patent No. 5,385,901, filed Oct. 2, 1992, issued Jan. 31, 1995 ("Kaplan") (Ex. 1003).

| References | Statutory Basis | Challenged Claims |
|---|---|---|
| Piper in view of Kaplan, Agrawal (Ex. 1004),[3] and WO '085 (Ex. 1005)[4] | § 103 | 2–6, 10 |
| Piper in view of Kaplan, Agrawal, and Keith (Ex. 1006)[5] | § 103 | 2–6, 10 |

In addition, Petitioner supports its challenges in the Petition with the Declaration of Clayton H. Heathcock, Ph.D. (Ex. 1007). Pet. 11.

## II. ANALYSIS

### *A. Claim construction*

For *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the patent specification. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

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[3] Agrawal et al., *Structure activity relationship studies of thalidomide analogs as anti-inflammatory and immunosuppressive agents*, 49(4) INT'L J. OF LEPROSY 512 (1981) ("Agrawal") (Ex. 1004).

[4] D'Amato et al., WO 94/20085, published Sept. 15, 1994 ("WO '085") (Ex. 1005).

[5] Keith & Walters, NATIONAL TOXICOLOGY PROGRAM'S CHEMICAL SOLUBILITY COMPENDIUM (Lewis Publishers, Inc. 1992) ("Keith") (Ex. 1006).

Petitioner presents chemical names and structures for the different compounds recited in claims 3–6 and 8–10 of the '517 patent. Pet. 13–16. Patent Owner does not dispute those names and structures. Prelim. Resp. 4–5. We are persuaded that the chemical names and structures provided in the Petition (Pet. 15–16) in relation to those compounds correspond to the ordinary and customary meaning of the recited terms as understood by one of ordinary skill in the art, consistent with disclosures in the specification.

Notably, all compounds recited in the challenged claims contain an amino group ($-NH_2$) on the benzene ring of the compound. *Id.*; Ex. 1001, claims 1–10. We determine that other claim terms need not be construed explicitly for purposes of this Decision.

*B. Asserted ground of obviousness of claims 1 and 7–9 over Piper (Ex. 1002) and Kaplan (Ex. 1003)*

Petitioner contends that claims 1 and 7–9 of the '517 patent would have been obvious over Piper and Kaplan. Pet. 24–36. Petitioner contends that "one of ordinary skill in the art would have readily combined the teachings of Piper and Kaplan to develop thalidomide analogs having one or both of [anti-inflammatory and immunosuppressive] functional activities for use in effectively treating at least [erythema nodosum leprosum] by reducing TNFα." Pet. 32–33 (citing Ex. 1007 ¶¶ 112–115). Petitioner also contends that one would have reasonably expected "Piper's amino-thalidomide analogs AH 14 and AH 13 to successfully exhibit the same activity as their common parent compound (thalidomide) because AH 14 and AH 13 have high structural similarity to the parent and also exhibit at least one key activity of the parent (i.e., anti-inflammation or immunosuppression)." Pet. 33–35 (citing Ex. 1007 ¶¶ 116–128).

*1. Piper (Ex. 1002)*

Piper discloses that thalidomide is effective in controlling erythema nodosum leprosum ("ENL") reactions in lepromatous leprosy. Ex. 1002, 511, 1st col. Piper states that ENL has two clinically relevant cites of action: (1) an anti-inflammatory cite of action, detectable in a "carrageenan" assay in rats, and (2) an immunosuppressive site of action, detectable in a plaque forming cells ("PFC") assay in mice. Using those two assays, Piper screened "[a]pproximately 50 thalidomide analogs." *Id.* at 511, 2nd col.

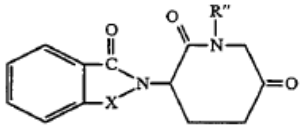
Discussing over 40 different analogs in particular, Piper states that it screened "[t]hirteen α-substituted glutarimides with changes in the 6 membered phthalimide moiety." *Id.* In this context, in addition to other compounds, Piper discusses "[f]our compounds involv[ing] electron donating substitutions (amino- or hydroxyl-) on the 6 membered phthalimide system." *Id.* Regarding those four compounds, Piper states that "three are active in carrageenan (4-hydroxythalidomide or AH 20, 3-hydroxythalidomide or AH 22, and 4-aminothalidomide or AH 13)," and "[o]ne, AH 20, is active in PFC and one, 3-aminothalidomide or AH 14, enhances PFC." *Id.* Thus, according to Piper, AH 22 (3-hydroxy) and AH 13 (4-amino) are "active" in the carrageenan assay, i.e., exhibit anti-inflammatory activity, AH 20 (4-hydroxy) is "active" in both assays, and AH 14 (3-amino) "enhances PFC." *Id.*

Piper also discusses "[t]wo compounds represent[ing] changes in the 5 membered ring system of the phthalimide moiety and two involv[ing] major alterations of the phthalimide system." *Id.* Two out of those four compounds, "EM 12 and glutethimide, are active in carrageenan." *Id.*

Although a number of disclosed compounds are active in only one or neither assay, Piper states, in addition to AH 20, that a "pyridine N-oxide-substituted phthalimide, AH 3, has activity in both systems." *Id.* Piper also teaches that D,L-thalidomide and D-thalidomide are active in both assays, although L-thalidomide is only active in the PFC assay. *Id.* at 512, 1st col.; *see also* Prelim. Resp. 23 (contending that D-thalidomide, AH 3, and AH 20 were active in both assays, but "[f]or the remaining compounds, some were active in one but not both assays, while some were inactive in both."). Piper does not mention TNFα. Ex. 1002, 511–12.

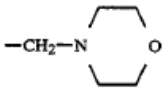
*2. Kaplan (Ex. 1003)*

Kaplan discloses methods for treating toxic concentrations of TNFα using thalidomide and certain analogs of thalidomide, such as "preferred compounds" encompassed by formula II:



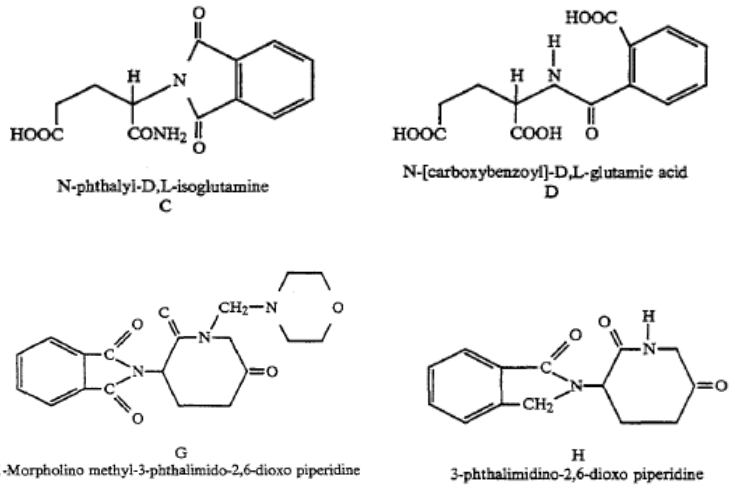
II

wherein X is $CH_2$ or C═O; R is H, $—CH_2CH_3$, $—C_6H_5$, $—CH_2C_6H_5$, $—CH_2CH═CH_2$, or



and hydrolysis products of said compounds wherein R is H and the peperidino ring or both the peperidino and the imido ring are hydrolyzed.

Ex. 1003, 4: 4–26. Kaplan teaches that "[e]specially preferred compounds" are compounds A–H, which include compounds C, D, G, and H depicted below.




*Id*. at 4:26–5:39. The parties do not dispute that compound H corresponds to EM 12 in Piper. Pet. 30; Prelim. Resp. 30.

Figures 1–4 in Kaplan show results of assays testing the effect of thalidomide and/or a TNFα inhibitor pentoxyfylline ("PTN") on induced TNFα production, protein synthesis by human peripheral blood monocytes, levels of different cytokines, and inhibition of reverse transcriptase production. Ex. 1003, 8:29–10:48. Figures 5–7 show results in assays measuring the inhibition of reverse transcriptase ("RT") production, for example in cells stimulated with TNFα, comparing the effect of thalidomide and PTN with compounds C, D, G, and H. *Id*. at 10:49–60.

Figure 5 indicates that compound G presents the highest percent of RT inhibition, and compound D presents the second highest. *Id*. at Fig. 5. Figures 6 and 7 present more variable results in relation to compounds C, D, G, and H, as compared to thalidomide, but in all three figures, compound G presents the highest percentage inhibition activity. *Id*. at Figs. 5–7.

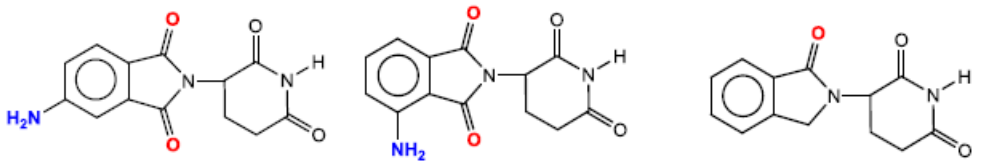
In its background section, Kaplan teaches that "thalidomide has long been employed for the treatment of erythema nodosum leprosum (ENL)," among other diseases. *Id*. at 2:42–55. Additionally, Kaplan discloses that

TNFα is "one of several cytokines released mainly by mononuclear phagocytes together with several other cytokines in response to stimuli to the immune system." *Id*. at 2:56–59; *see also id*. at 3:41–49 (stating that TNFα, IL-1, IL-6, IL-8, GM-CSF "are necessary for a proper immune response" and "produced by mononuclear phagocytes," and "[s]till other cytokines are produced by the T-cells"). In addition to being associated with the destruction of tumor cells, and present "in response to immunostimulators such as bacterial and viral infections," TNFα "is markedly elevated in ENL." *Id*. at 2:60–3:2.

Kaplan teaches that toxicity associated with TNFα is observed in conditions such as cachexia, septic shock, and infections with retroviruses (e.g., HIV). *Id*. at 3:3–40. Kaplan further discloses that "antiinflammatory and immunosuppressive steroids such as prednisolone and dexamethasone have been employed to treat the debilitating effects of TNFα," but those "agents also block the production of other cytokines so that the patients become susceptible to life threatening infections." *Id*. at 3:50–55.

*3. Analysis*

We agree with Petitioner that Piper discloses, among other thalidomide analogs, the three compounds known as 3-aminothalidomide (AH 14), 4-aminothalidomide (AH 13), and EM-12, which have the following chemical structures.



Pet. 3, 27–28. Petitioner persuades us that the composition recited in claim 8 corresponds to AH 14, and, therefore, compositions recited in method claims 1, 7, and 8 encompass AH 14. Pet. 29. Petitioner also persuades us that the composition recited in claim 9 corresponds to AH 13, and, therefore, compositions recited in method claims 1, 7, and 9 encompass AH 14. *Id*.

As noted above, both Piper and Kaplan teach that thalidomide is effective to treat ENL reactions in leprosy. Piper teaches that ENL involves two cites of action, i.e., anti-inflammatory activity (measured by the carrageenan assay) and immunosuppressive activity (measured by the PFC assay). Piper teaches that most of the 50 screened analogs are active in only one or neither assay. Piper teaches that thalidomide itself, as well as two analogs, AH 3 and AH 20, are active in both assays. None of those three compounds contains an amino group on the benzene ring, as required by each of the challenged claims. *See* Prelim. Resp. 23 (presenting chemical structures).

Petitioner refers us to two compounds in Piper (of the 50 screened) as analogs having an amino group on the benzene ring, AH 13 and AH 14. Pet. 26–28. Petitioner and Patent Owner agree that AH 13 is active in only one assay, the carrageenan (anti-inflammatory) assay. Pet. 26; Prelim. Resp. 29. Petitioner asserts that AH 14 is only active in the other assay, the PFC (immunosuppressive) assay, but Patent Owner contends that AH 14 actually is active in neither assay. Pet. 26; Prelim. Resp. 13, 28–29. Evidence cited by Patent Owner persuades us that AH 14 is inactive in both assays—that the statement in Piper that AH 14 "enhances PFC" means that AH 14 is immunostimulatory, not immunosuppressive. *Id*. at 28–29 (citing Ex. 1002, 511; Ex. 2029, 69–70).

Petitioner agrees that Kaplan does not disclose thalidomide analogs having an amino group on the benzene ring, but points to EM 12, also disclosed in Piper, called compound H in Kaplan. Pet. 30; Ex. 1002, 511, 2nd col.; Ex. 1003, 5:30–39. EM 12 contains no amino group on the benzene ring, but contains one C=O on the 5-carbon ring. Pet. 28, 30–31. Petitioner contends that Kaplan teaches a method of inhibiting TNFα production by administering EM 12, citing claim 1 in Kaplan (Ex. 1003), which recites a compound encompassing EM 12. Pet. 30. Petitioner also contends that Kaplan indicates that EM 12 is one of eight "[e]specially preferred" analogs disclosed in the reference. *Id*. at 31; Ex. 1003, 4:27–5:39.

Independent claim 1 and dependent claims 7–9 of the '517 patent recite methods of reducing TNFα levels in a mammal by administering certain thalidomide analogs having an amino group on the benzene ring. As Patent Owner points out, Piper does not mention TNFα. Prelim. Resp. 19; Ex. 1002, 511–12. Consequently, Petitioner necessarily combines certain teachings in Piper (disclosing AH 13 and AH 14, each having an amino group on the benzene ring) with those in Kaplan (disclosing methods of inhibiting TNFα using different thalidomide analogs). As such, Petitioner's contentions regarding reasons to combine relevant teachings from the two references, as well as assertions regarding a reasonable expectation of success in performing recited methods, are critical to our analysis. Pet. 32–35.

*a) Alleged Reasons to Combine Piper and Kaplan*

Petitioner contends that disclosures in Piper and Kaplan "would have been easily combined by one of ordinary skill" because "each one teaches the same parent compound (thalidomide) and various analogs thereof in

relation to treating the same condition (ENL)." Pet. 32–33 (citing Ex. 1007, ¶¶ 112–115). We are not persuaded, however, that Piper sufficiently teaches or suggests that AH 13, AH 14, or EM 12 would be useful to treat ENL. Piper discloses that ENL involves two mechanisms of action, and, therefore, suggests that compounds exhibiting both activities (as measured in the two assays) might be useful to treat ENL. Such compounds include D, L- and D-thalidomide (expressly disclosed in Piper as useful to treat ENL), AH 3, and AH 20. We are not persuaded that Piper teaches or suggests sufficiently that any other disclosed compounds active in only one or neither assay, such as AH 13, AH 14, or EM 12, would have been effective in treating ENL.

In addition, Patent Owner persuades us that Kaplan does not teach treating ENL with any compound other than thalidomide itself. Prelim. Resp. 16–17. Kaplan does not describe using any of the disclosed analogs, e.g., any of compounds A–H, such as EM 12, to treat ENL. Rather, at most, in its background section, Kaplan states that "thalidomide has long been employed for the treatment" of ENL, as well as other diseases, and that TNFα "is markedly elevated in ENL." Ex. 1003, 2:42–55, 3:1–2.

Petitioner contends that Kaplan teaches using EM 12 to reduce TNFα levels, and both Piper and Kaplan "teach the well-known analog EM 12, and that anti-inflammatory and immunosuppressive properties are important to the efficacy and activity of thalidomide and its analogs." Pet. 30–33 (citing Ex. 1007 ¶¶ 90–120). Thus, according to Petitioner, "one of ordinary skill in the art would have readily combined the teachings of Piper and Kaplan to develop thalidomide analogs having one or both of these important functional activities for use in effectively treating at least ENL by reducing TNFα." *Id.*

We agree with Petitioner that both Piper and Kaplan disclose EM 12 and at least Piper suggests that both "anti-inflammatory and immuno-suppressive properties are important to the efficacy and activity of thalidomide and its analogs." *Id*. As discussed above, however, we are not persuaded that Piper discloses sufficiently that EM 12, which exhibits only anti-inflammatory activity in Piper, would have been useful to treat ENL. Moreover, while Kaplan suggests that EM 12 may be useful to reduce TNFα levels, Kaplan, alone or in combination with Piper, does not suggest sufficiently that a thalidomide analog containing an amino group on the benzene ring (in contrast to compounds, including EM 12, disclosed in Kaplan) would be useful to reduce TNFα levels.

Piper, which discusses ENL, does not mention TNFα, nor does it establish a relationship between results from the two assays regarding ENL's two sites of action (carrageenan and/or PFC) and TNFα levels. Prelim. Resp. 19–20. Kaplan, at most, states that thalidomide is useful to treat ENL and reduce TNFα levels, and that TNFα levels are "markedly elevated in ENL." Ex. 1003, 2:42–45, 3:1–2. Nonetheless, and even if Kaplan also suggests that EM 12 may reduce TNFα levels, the reference does not suggest sufficiently that by doing so, EM 12 would be useful to treat ENL. In addition, while Piper discloses EM 12 (among many analogs), and may indicate that this analog is active in the carrageenan assay (i.e., has at least some anti-inflammatory activity), we agree with Patent Owner that neither Piper nor Kaplan (which is silent on the two Piper assays) establishes sufficiently that anti-inflammatory activity alone by any analog (such as AH 13) necessarily corresponds to an ability to reduce TNFα levels.

Additional information cited by Patent Owner further persuades us that Petitioner does not establish sufficiently that a link exists between treating ENL and reducing TNFα levels. For example, Patent Owner provides information indicating that EM 12, which Kaplan suggests may reduce TNFα, only "has ***marginal activity*** in the carrageenan assay with activity at the highest dose tested but ***no activity*** in lower doses, and it ***lacks activity*** in the PFC assay." Prelim. Resp. 43–44 (citing Ex. 2028, 673, 1st col.; Ex. 2029, 70). Such evidence runs counter to the notion that an ordinary artisan would have understood that one could treat ENL by using any thalidomide analog (such as EM 12) that reduces TNFα, as Petitioner suggests. Pet. 33.

Furthermore, as noted by Patent Owner and stated in Kaplan, immune responses involve a number of different biological molecules, including cytokines such as IL-1, IL-6, IL-8, GM-CSF, as well as other cytokines produced by T-cells, in addition to TNFα. As Patent Owner notes, "some anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), actually ***increase*** TNFα production in rheumatoid synovia and whole blood." Prelim. Resp. 22 (citing Ex. 2020, Abstract). Information before us, therefore, fails to establish sufficiently a correlation between anti-inflammatory activity (as measured in the carrageenan assay in Piper) with a reduction in TNFα levels in particular, even assuming the references indicate that EM 12 does both things.

Lastly, as noted by Patent Owner, data in Kaplan suggests that compound G works better than EM 12 to inhibit TNFα, indicating that Kaplan does not favor using EM 12 in particular. Ex. 1003, Figures 5–7; Prelim. Resp. 33–34.

Thus, at most, Piper and Kaplan together indicate that thalidomide is useful to both treat ENL and reduce TNFα levels, and EM 12 (and other analogs lacking the amino group on the benzene ring) may reduce TNFα, even if EM 12 exhibits activity in only one out of two relevant sites of action for ENL. Petitioner does not establish sufficiently that an ordinary artisan reading those two references would have had reason to pick AH 13 or AH 14 (out of over 40 analogs discussed in Piper) in particular for use in a method to reduce TNFα levels (disclosed in Kaplan in relation to different analogs).

*b) Alleged Reasonable Expectation of Success*

Petitioner also contends that an ordinary artisan would have reasonably expected Piper's AH 14 and AH 13 to exhibit the same activity as thalidomide because AH 14 and AH 13 have high structural similarity to that parent compound and exhibit "at least one key activity of the parent (i.e., anti-inflammation or immunosuppression)." Pet. 33. In support, Petitioner refers to EM 12 and its activities (as shown in Piper and Kaplan), and cites Dr. Heathcock's Declaration for the proposition that "those of ordinary skill may expect compounds of high structural similarity that have an important functional activity in common to have other activities in common as well." Pet. 34 (citing Ex. 1007, ¶¶ 118, 119). We note that other than referring to Piper and Kaplan generally, the cited paragraphs in Dr. Heathcock's Declaration cite no evidence in support of that proposition. Ex. 1007, ¶¶ 118, 119.

Other information of record before us, by contrast, indicates that even the smallest of chemical differences in thalidomide analogs impacts biological activity. Teachings in Piper alone indicate that different analogs,

even those differing only by the addition and/or location of a single "electron donating" group on the benzene ring, exhibit different activities. Piper discusses "[t]hirteen α-substituted glutarimides with changes in the 6 membered phthalimide moiety." Ex. 1002, 511, 2nd col. Of those, many are active in one or the other assay (carrageenan or PFC) or neither assay. Among those thirteen, Piper also discusses "[f]our compounds involv[ing] electron donating substitutions (amino- or hydroxyl-) on the 6 membered phthalimide system." *Id*. Among those four compounds, and even among the two compounds containing an amino group on the 6-carbon benzene ring (AH 13 and AH 14), Piper found differing results in the two assays. For example, Piper states that AH 13 is active in the carrageenan assay but not the PFC assay, while AH 14 "enhances PFC" and is inactive in the carrageenan assay. *Id*.; *see also* Prelim. Resp. 29 (noting differing assay results for thalidomide and different analogs, including those with a hydroxyl group on the benzene ring, AH 22 and AH 20).

Thus, Patent Owner persuades us, consistent with binding case law, that "even minor structural modifications to a chemical compound can have significant and highly unpredictable effects on functionality," as evidenced by Piper and other references of record here. Prelim. Resp. 26–27 (citing relevant Federal Circuit and other case law) (citations omitted). We are not persuaded by Petitioner's contention that "those of ordinary skill may expect compounds of high structural similarity that have an important functional activity in common to have other activities in common as well." Pet. 34.

When arguing a reasonable expectation of success, Petitioner also contends that "by disclosing steroids [prednisolone and dexamethasone] that exhibit anti-inflammation, immunosuppression, and TNFα inhibition,

Kaplan identifies another direct relationship—i.e., between compounds that are anti-inflammatory or immunosuppressive and compounds that block TNFα." Pet. 34–35 (citing Ex. 1007 ¶ 120 (citing Ex. 1003, 3:50–55)). Petitioner does not contend, however, that either steroid is a thalidomide analog. In addition, Kaplan teaches that those steroids exhibit *both* anti-inflammatory and immunosuppressive activities, similarly to thalidomide, but unlike EM 12 (as disclosed in Piper). In any event, Kaplan's discussion about steroids unrelated in structure does not indicate sufficiently that one would have expected entirely different compounds (e.g., AH 13 or AH 14) to reduce TNFα levels.

*4. Conclusion*

For the reasons discussed above, Petitioner has not established a reasonable likelihood of prevailing on the ground that claims 1 and 7–9 of the '517 patent would have been obvious over Piper in view of Kaplan.

*C. Asserted ground of obviousness of claims 2–6 and 10 over Piper, Kaplan, Agrawal (Ex. 1004), and WO '085 (Ex.1005)*

Petitioner contends that claims 2–6 and 10 of the '517 patent would have been obvious over Piper, Kaplan, Agrawal, and WO '085. Pet. 37–52. In relation to Piper and Kaplan, Petitioner raises similar contentions to those discussed above. *Id*. at 39–40. Petitioner additionally relies on Agrawal (published alongside Piper), which discusses carrageenan and PFC assay results using thalidomide analogs, and WO '085, which discloses methods of inhibiting angiogenesis using thalidomide and thalidomide analogs. *Id*. at 40–42. Petitioner again contends that an ordinary artisan would have had reason to combine teachings in those references to reach the recited methods

and compounds, and one would have had a reasonable expectation of success in doing so. *Id*. at 43–49.

*1. Agrawal (Ex. 1004)*

Like Piper, Agrawal describes a study in an effort to develop thalidomide analogs that are effective in controlling ENL—again using the carrageenan (anti-inflammatory) and PFC (immunosuppressive) assays. Agrawal discusses many different analogs, including "analogs containing $NO_2$, COOH, $NH_2$, or OH groups." Ex. 1004, 512, 2nd col. In this context, Agrawal states that "agents containing the electron donating groups such as 3 or 4-hydroxy and 4-aminothalidomide retained the anticarrageenan activity, whereas the analogs with electron withdrawing groups such as 4-nitro or 4-carboxy were not active in this assay." *Id*. Agrawal goes on to state, however, that "the biological activity in the PFC assay did not correlate with electronic properties since not only the 4-nitro and 4-carboxy analogs but also the 4-hydroxythalidomide was active in this system." *Id.*

Thus, consistent with teachings in Piper, Agrawal indicates that 4-hydroxythalidomide (AH 20) is active in both assays, and 3-hydroxy-thalidomide (AH 22) and 4-aminothalidomide (AH 13) are active only in the carrageenan assay. While it does not discuss 3-aminothalidomide (AH 14) per se, teachings in Agrawal also are consistent with the fact that AH 14 is inactive in both assays, as indicated in Piper.

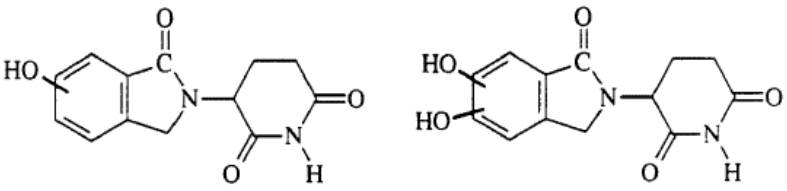
Agrawal also states that study results "suggest that modifications in the parent thalidomide molecule can be made which retain the anti-inflammatory *and* immunosuppressive activity, but yet may be expected to alter the neurotoxic and teratogenic properties." *Id*. (emphasis added). Like Piper, therefore, Agrawal suggests that thalidomide analogs that exhibit both

anti-inflammatory and immunosuppressive activities (i.e., active in both assays) would be useful to treat EML.

*2. WO '085 (Ex. 1005)*

WO '085 discloses methods for preventing unwanted angiogenesis by administering thalidomide and "related compounds." Ex. 1005, 1:20–25.[6] As noted in WO '085, angiogenesis is the generation of new blood vessels into a tissue or organ. *Id*. at 1:28–29.

WO '085 discloses that "[s]pecific preferred compounds . . . of the present invention include thalidomide, its precursors, metabolites and analogs," and that "[p]articular analogs include EM-12, N-phthaloyl-DL-glutamic acid (PGA) or N-phthaloyl-DL-glutamine anhydride." *Id*. at 14:8–12. WO '085 discloses using "epoxides of thalidomide, EM-12 and EM-138" (*id*. at 16:1–15) and that the epoxides can be hydrolyzed to form six compounds, including the two compounds reproduced below.




*Id*. at 16:20–17:9. WO '085 further teaches that "the hydroxyl group can be on carbons 1, 2, 3, 4, 5 and 6 of the benzene ring." *Id*. at 17:10–11.

*3. Analysis—Claims 2–6*

Claims 2–6 of the '517 patent depend from claim 1, and recite methods of reducing TNFα in a mammal by administering compositions

[6] Page citations in relation to Ex. 1005 refer to pages numbers in the original document, located at the top of the reference.

corresponding to thalidomide analogs having an amino group on the benzene ring, and a single C=O in the 5-carbon ring.

In relation to those claims, Petitioner contends that Agrawal teaches a preference for amino-substituted analogs, as well as "a preference for analogs with an amino- or hydroxyl substituted benzo ring." Pet. 40–41 (citing Ex. 1004, 512, Ex. 1007 ¶¶ 87–89, 139 (similarly discussing and citing Agrawal)). We are not persuaded.

As discussed above, Agrawal, like Piper, discloses the testing of many thalidomide analogs and suggests that analogs exhibiting both anti-inflammatory and immunosuppressive activities (i.e., active in both the carrageenan and PFC assays) would be useful to treat ENL. Ex. 1004, 512; *see also* Pet. 41–42 (referring to that teaching in Agrawal). Both Piper and Agrawal indicate that 4-hydroxythalidomide (AH 20) is active in both assays, 3-hydroxy-thalidomide (AH 22) and 4-amino-thalidomide (AH 13) are active only in the carrageenan assay (not the PFC assay), and 3-amino-thalidomide (AH 14) is inactive in both assays. Thus, at most, both references suggest a preference, in the context of treating ENL, for an analog with a hydroxyl group at a specific location in the benzene ring (4-hydroxy, not 3-hydroxy), and no particular preference for analogs with an amino group on the benzene ring.

Petitioner contends that WO '085 "teaches that each of thalidomide, EM 12, and 3-, 4-, 5-, and 6-hydroxyl-substituted EM 12 inhibit angiogenesis," and that "EM 12 is a more potent inhibitor of angiogenesis than thalidomide." Pet. 42. Petitioner then contends that an ordinary artisan "would have readily combined the teachings" of the four cited references "to develop thalidomide analogs having an amino or hydroxyl-substituted benzo

ring, and at least one important functional activity of thalidomide (i.e., anti-inflammation or immunosuppression) for use in effectively treating at least ENL by reducing TNFα." *Id*. at 43–44 (citing Ex. 1007 ¶¶ 145–153).

Petitioner does not point us to anything in Agrawal or WO '085 that overcomes the deficiencies mentioned above in relation to Petitioner's assertion that an ordinary artisan would have combined the teachings of Piper and Kaplan to develop thalidomide analogs having an amino group on the benzene ring for use in reducing TNFα levels.

As discussed above, teachings in Agrawal and Piper are very similar and, at best, suggest a preference for an analog with a hydroxyl group at a specific location in the benzene ring (4-hydroxy, not 3-hydroxy), without sufficiently indicating a preference for analogs with an amino group on the benzene ring. In addition, Kaplan, the only cited reference to discuss methods of reducing TNFα, does not discuss, much less indicate a preference for, thalidomide analogs with an amino group on the benzene ring.

In relation to WO '085, Petitioner does not explain or reasonably support that inhibiting angiogenesis correlates to reducing TNFα. Even assuming Petitioner had established such a correlation, however, all four references in combination potentially would have suggested a preference for EM 12 or EM 12 containing a 4-hydroxyl group in the benzene ring. For the reasons discussed above, however, we are not persuaded that any of the four references, either alone or in combination, sufficiently suggests using a thalidomide analog containing an amino group on the benzene ring, whether to treat ENL, reduce TNFα, or inhibit angiogenesis.

Petitioner's discussion of WO '085 does not persuade us "that structural similarity is reasonably predictive of functional similarity." Pet. 42 (citing Ex. 1007 ¶¶ 94–96, 140–141). We likewise are not persuaded by Petitioner's assertions regarding a reasonable expectation of success, which again rely on contentions that an ordinary artisan "would have reasonably expected other structurally similar analogs of thalidomide and EM 12 to behave like their parent compounds." *Id*. at 44–45 (citing Ex. 1007 ¶¶ 155–165). As discussed above, information of record, such as Piper and Agrawal, indicates that one of ordinary skill would have known that even small chemical differences in thalidomide analogs impacted biological activity. For example, Piper and Agrawal indicate that the absence or presence, as well as the specific location, of a hydroxyl or amino group on the benzene ring impacts whether that analog exhibits anti-inflammatory and/or immunosuppressive activity (as tested in carrageenan and PFC assays).

In addition, as Petitioner concedes, neither Kaplan (the only reference discussing TNFα) nor WO '085 discloses the use of a thalidomide analog containing an amino group on the benzene ring. Pet. 47. As Petitioner also recognizes, no cited reference discloses the use of an EM 12 analog containing an amino group on the benzene ring. *Id*. For the reasons discussed above, we are not persuaded that any cited reference, either alone or in combination, reasonably suggests substituting a hydroxyl group with an amino group on the benzene ring to produce a thalidomide analog useful in reducing TNFα levels.

*4. Analysis—Claim 10*

We likewise are not persuaded that an ordinary artisan would have had sufficient reason to prepare any of the four compounds recited in claim 10. All four compounds in claim 10 comprise an amino group on the benzene ring (like AH 13 and AH 14) and a single C=O in the 5-carbon ring (like EM 12). Petitioner has not established sufficiently, with reasonable underpinnings, why one would have produced such compounds for any reason, for example to produce analogs that inhibit angiogenesis (discussed in WO '085). As Petitioner notes, none of the cited references disclose EM 12 (or other analog having a single C=O in the 5-carbon ring) modified to have an amino group on the benzene ring. Pet. 47. While WO '085 teaches a compound having a hydroxyl group on the benzene ring (like AH 20) and a single C=O on the 5-carbon ring (like EM 12), Petitioner does not explain sufficiently why one would substitute the hydroxyl group in that analog with an amino group.

For example, we are not persuaded that Petitioner contends or reasonably establishes a link between inhibiting angiogenesis (disclosed in WO '085), treating ENL (or anti-inflammatory and/or immuno-suppressive activities) (disclosed in Piper and Agrawal), and/or reducing TNFα (disclosed in Kaplan). Petitioner's general arguments regarding the "known activities and structures of thalidomide, EM 12, and structurally similar amino- and hydroxyl-substituted analogs thereof" do not establish that link, nor reasonably provide a reason to make the specific hydroxyl to amino substitution needed here.

Piper and Agrawal disclose that AH 20 (4-hydroxythalidomide), but not AH 22 (3-hydroxylthalidomide), exhibits both anti-inflammatory *and*

immunosuppressive activities (both sites of action for ENL). Ex. 1002, 511, 2nd col. Kaplan discloses EM 12 (Ex. 1003, 5:30–39), and WO '085 discloses EM 12 with a hydroxyl group on any of carbons 1, 2, 3, 4, 5 and 6 of the benzene ring (Ex. 1005, 17). Thus, at most, even if we assume a link exists between treating ENL, reducing TNFα, and/or inhibiting angiogenesis, the four references would have led an ordinary artisan to make a specific version from a genus disclosed in WO '085, i.e., a species of EM 20 modified to include a hydroxyl group at the same location in the benzene ring as AH 20. For the same reasons discussed above, Petitioner's assertion that "known activities and structures of thalidomide, EM 12, and structurally similar amino- and hydroxyl-substituted analogs" would have provided a reason to prepare a thalidomide analog having an amino group on the benzene ring is not supported reasonably by information before us. Pet. 43.

Furthermore, we are not persuaded that the compounds of claim 10 correspond to only a "few known options" of possible relevant thalidomide analogs, as Petitioner contends. Pet. 48. As noted by Patent Owner, the cited references disclose a large number of possible thalidomide analogs. *See* Prelim. Resp. 42 n.15 ("WO '085 alone discloses billions of thalidomide analogs," "Kaplan discloses over one hundred," "Piper discloses 'approximately 50 thalidomide analogs,'" and "Agrawal discloses various modifications suggesting hundreds of additional analogs") (citations omitted). Of those many possible thalidomide analogs, the cited references suggest that a subset of analogs—analogs lacking an amino group on the benzene ring—may be useful to treat ENL, reduce TNFα, or inhibit angiogenesis. Information before us does not establish adequately that one of ordinary skill in the art would have had reason to modify one specific

analog disclosed in WO '085 (out of many) to prepare the specific "four amino-substituted EM 12 analogs" recited in claim 10. Pet. 48.

*5. Conclusion*

For the reasons discussed above, Petitioner has not established a reasonable likelihood of prevailing on the ground that claims 2–6 and 10 of the '517 patent would have been obvious over Piper in view of Kaplan, Agrawal, and WO '085.

*D. Asserted ground of obviousness of claims 2–6 and 10 over Piper, Kaplan, Agrawal, and Keith (Ex.1006)*

Petitioner contends that claims 2–6 and 10 of the '517 patent would have been obvious over Piper, Kaplan, Agrawal, and Keith. Pet. 52–59. In relation to Piper, Kaplan, and Agrawal, Petitioner asserts similar contentions to those discussed above. *Id*. at 52–55. In this ground, Petitioner additionally relies on Keith, which, as Petitioner notes, discloses "solubility information for a variety of chemical compounds, including thalidomide and EM 12." Pet. 55 (citing Ex. 1006 at 190, 397).

Petitioner does not explain adequately how Keith overcomes the deficiencies mentioned above in relation to Petitioner's assertion that an ordinary artisan would have combined the teachings of Piper, Kaplan, and Agrawal—deficiencies equally applicable to the assertion in this ground—to practice the methods of claims 2–6, or prepare the specific compounds recited in claim 10.

At most, Petitioner argues, based on Keith, that an ordinary artisan would have known that thalidomide and EM 12 "are practically insoluble in water." Pet. 55 (citing Ex. 1007 ¶ 178). Petitioner also contends, citing conclusory statements by Dr. Heathcock in support, that "increasing the

solubility of a drug can significantly enhance its bioavailability," and that an ordinary artisan "would have generally known that the addition of an electron donating substituent (e.g., an amino or hydroxyl group) to the benzo ring of EM 12 would likely increase its solubility." *Id*. (citing Ex. 1007 ¶¶ 178, 187). Thus, according to Petitioner, "one would have been driven to aminate EM 12 in order to improve its poor solubility." *Id*. at 55–56 (citing Ex. 1007 ¶¶ 178, 187–188).

For all the reasons discussed above, information before us does not suggest or point adequately to modifying EM 12 or another relevant compound to contain an amino group on the benzene ring. Keith does not overcome that deficiency by merely disclosing the solubility of EM 12 and thalidomide. Even assuming one would have had reason to prepare a more soluble thalidomide analog, Patent Owner persuades us that an ordinary artisan would have faced "a potentially limitless list of modifications," without sufficient guidance pointing to the addition of an amino group on the benzene ring in particular. Prelim. Resp. 54–55.

For the reasons discussed above, Petitioner has not established a reasonable likelihood of prevailing on the ground that claims 2–6 and 10 of the '517 patent would have been obvious over Piper in view of Kaplan, Agrawal, and Keith.

## III. CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence does not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1–10 of the '517 patent.

## IV. ORDER

It is

ORDERED that the Petition is *denied* and no trial is instituted.

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# EXHIBIT 2

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June 10, 2009



**VIA HAND DELIVERY**

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Enforce the FDC Act to Prevent the Use of REMS to Block or Delay Generic Competition**

Dear Sir or Madam:

**CITIZEN PETITION**

Dr. Reddy's Laboratories, Inc. ("Dr. Reddy's") submits this Citizen Petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") and the Food and Drug Administration's ("FDA's") implementing regulations at 21 C.F.R. § 10.30 to request that FDA establish procedures to facilitate the availability of generic versions of drug products subject to a Risk Evaluation and Mitigation Strategy ("REMS") and enforce the FDC Act to prevent companies from using REMS to block or delay generic competition. Dr. Reddy's also requests that FDA work with the Federal Trade Commission ("FTC") in an effort to prevent anti-competitive REMS abuses.

As discussed below, Dr. Reddy's is concerned that REMS, which were created under the FDA Amendments Act, Pub. L. No. 110-85 (enacted Sept. 27, 2007) ("FDAAA"), while a useful tool to "ensure that the benefits of the drug outweigh the risks of the drug," FDC Act § 505-1(a)(1), can also be used improperly to prevent or delay generic competition. Specifically, REMS can be used as an excuse by New Drug Application ("NDA") sponsors for providing generic companies with drug product sample needed to conduct bioequivalence testing and for other purposes required by FDA. Dr. Reddy's recent experience in attempting to obtain biostudy sample of a drug product under a so-called "deemed REMS" has borne out this concern. In that case, after sending multiple requests to purchase biostudy drug product sample, Dr. Reddy's was ultimately told by the NDA holder that the company "has no obligation to supply Dr. Reddy's . . . and declines to do so."

FDA-2009-P-0266-0001

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The number of drug products subject to REMS is growing.[1] And unless FDA takes swift action now by exercising the authority that Congress granted the Agency under the FDC Act to prevent REMS gaming, consumers will be prevented from having timely access to generic versions of an increasing number of important drugs. Moreover, the use of REMS to prevent generic competition upsets the careful balance Congress intended when it passed the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) ("Hatch-Waxman Amendments") by permitting an additional *de facto* and unearned period of market exclusivity to NDA holders.

## I. ACTION REQUESTED

This Citizen Petition requests that FDA:

(1) Promptly issue a Compliance Policy Guide ("CPG") or guidance document establishing a procedure whereby a generic applicant who seeks to obtain a sufficient quantity of a listed drug subject to a REMS (that incorporates elements to assure safe use that restrict product distribution) to conduct bioequivalence testing (and to meet other FDA requirements) can obtain a letter from FDA describing the Agency's findings that such generic applicant has agreed to applicable restrictions on distribution of the listed drug necessary to assure safe use of the drug product during bioequivalence testing;

(2) Incorporate into REMS that restrict product distribution, including those REMS currently under review for "deemed REMS" products, a provision stating that the listed drug sponsor will not to use REMS restricted distribution elements to assure safe use to delay or block generic competition;

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[1] FDA has approved 49 REMS for new drugs approved since the enactment of FDAAA, and has requested REMS for many other products. See FDA, Approved REMS, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm (last updated May 30, 2009). In addition, pursuant to FDAAA § 909(b)(1), many products approved prior to the enactment of FDAAA are deemed to have in effect an ***approved*** REMS. See FDA, Notice, Identification of Drug and Biological Products Deemed to Have REMS for Purposes of FDAAA of 2007, 73 Fed. Reg. 16,313 (Mar. 27, 2008) ("Drug and biological products deemed to have in effect an approved REMS are those that on March 25, 2008 . . . had in effect 'elements to assure safe use.'"). Sponsors of "deemed REMS" products were required to submit a proposed REMS to FDA by September 21, 2008. See FDAAA § 909(b)(3).

(3) Enforce the FDC Act against sponsors of listed drugs subject to an approved restricted distribution REMS, including, to the extent possible, against those sponsors of "deemed REMS" products who, notwithstanding having received a copy of a letter identified in (1) above, have refused (either explicitly or constructively) to sell, at fair market value, a sufficient quantity of their drug product to a proposed generic applicant for bioequivalence testing purposes; and

(4) Refer to the FTC any complaints received from generic drug manufacturers alleging that the sponsor of a listed drug subject to an approved restricted distribution REMS has used such REMS in an anti-competitive manner to delay or block generic competition.

## I. STATEMENT OF GROUNDS

### A. Factual Background

#### 1. FDA Approval of Generic Drugs

Under the FDC Act, as amended by the Hatch-Waxman Amendments, in order for FDA to receive an Abbreviated New Drug Application ("ANDA") for a proposed generic version of an innovator drug product, the Agency requires that the application contain, among other things, information showing that the proposed generic drug product is "bioequivalent" to the drug identified in the Orange Book as the Reference Listed Drug ("RLD"). See FDC Act §§ 505(j)(2)(A)(iv), 505(j)(4)(F); 21 C.F.R. §§ 314.94(a)(7), 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referenced in the ANDA). A generic drug product is bioequivalent to the RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either single dose or multiple doses." FDC Act § 505(j)(8)(B)(i).

The purpose of demonstrating bioequivalence is to determine whether changes in a proposed drug product's formulation or manufacturing affect the rate or extent to which the active ingredient reaches the primary site of action. It is presumed that a drug product containing the identical active ingredient will behave in the same way as the RLD if it reaches the primary site of action at the same rate and to the same extent as the RLD. See

21 C.F.R. § 320.1(e). FDA has considerable discretion in establishing the appropriate drug product-specific methods for a generic applicant to demonstrate bioequivalence. For products that because of their inherent toxicity could be harmful, Dr. Reddy's understands that FDA typically determines that an effective way to ensure the safety of subjects in proposed investigations regarding the bioequivalence of such drugs is to require generic applicants to submit an Investigational New Drug Application to the Office of Generic Drugs ("OGD"), or to otherwise provide OGD with sufficient assurance that the bioequivalence study will be conducted in such a manner as to ensure the safety of the study subjects. Such safeguards, Dr. Reddy's understands, represent a permissible substitute for controls present under a REMS.

In vivo testing is FDA's preferred method for an ANDA applicant to demonstrate bioequivalence (and for a 505(b)(2) applicant to measure bioavailability[2]), but it is not the only permissible method. FDA's regulations state that "[b]ioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods," which are described at 21 C.F.R. § 320.24 in descending order of accuracy, sensitivity, and reproducibility.

In addition to conducting any required bioequivalence testing between a proposed generic drug product (i.e., test article) and the RLD, FDA's regulations require the responsible party conducting bioequivalence testing to retain a reserve sample of each test article and RLD used to perform in vivo or in vitro bioequivalence studies that is representative of each batch of the test article and RLD used for testing. See 21 C.F.R. §§ 320.38, 320.63. The reserve samples must "consist of a sufficient quantity to permit FDA to perform five times all of the release tests required in the application or supplemental application." Id. § 320.38(c).

For many drug products, a sufficient amount of the RLD for a generic applicant to conduct FDA-required bioequivalence testing (as well as retained samples) can be procured using normal distribution channels; for example, through drug product wholesalers. A drug product under a REMS, however, may be subject to certain distribution restrictions that significantly limit drug product availability and prevent a prospective generic applicant from obtaining a sufficient quantity of the drug product to conduct required bioequivalence testing and for retained samples. For example, Celgene Corporation's ("Celgene's") REVLIMID (lenalidomide) Capsules and THALOMID

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[2] Although this Citizen Petition is specifically directed at generic applicants seeking approval of an ANDA, the issues identified in this petition are also relevant to 505(b)(2) applicants who plan to rely on FDA's previous findings of safety and effectiveness for a listed drug.

(thalidomide) Capsules, both of which are "deemed REMS" products[3] and are known human teratogens, are tightly controlled under detailed restricted distribution programs. In the case of REVLIMID, that program is known as the RevAssist℠ program. Under the RevAssist℠ program, REVLIMID is prescribed, received, and dispensed only after the physician, patient, and pharmacy involved are all registered in the program. REVLIMID is not distributed through wholesalers and is not given to physicians via samples. In the case of THALOMID, the restricted distribution program is known as the S.T.E.P.S.® program (i.e., System for Thalidomide Education and Prescribing Safety). As with the REVLIMID RevAssist℠ program, THALOMID, under the S.T.E.P.S.® program, is prescribed, received, and dispensed only after the physician, patient, and pharmacy involved are all registered in the program. THALOMID is similarly not distributed through wholesalers and is not given to physicians via samples.

### 2. REMS Requirements and Elements to Assure Safe Use

FDAAA amended the FDC Act to add § 505(p), which states:

> A person may not introduce or deliver for introduction into interstate commerce a new drug if –
>
> (A)(i) the application for such drug is approved under [FDC Act § 505(b) or (j)] and is subject to section 503(b) . . . and
>
> (B) a [REMS] is required under section 505-1 with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 505-1, including requirements regarding assessments of approved strategies.

FDC Act § 505(p).

FDC Act § 505-1 provides FDA with the authority to require a proposed REMS from an NDA sponsor if the Agency determines that such a strategy "is necessary to ensure that the benefits of the drug outweigh the risks of the drug." FDC Act § 505-1(a)(1). FDA may also require a REMS for a previously approved covered application if the Agency "becomes aware of new safety information and makes a determination that

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[3] Pursuant to FDAAA § 909, all drug products approved before March 25, 2008 with elements to assure safe use (either required under 21 C.F.R. § 314.520, or otherwise agreed to by the sponsor) are deemed to have in effect an approved REMS. See 73 Fed. Reg. at 16,314 (Mar. 27, 2008).

such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug." Id. § 505-1(a)(2).

Under FDC Act § 505-1(f), FDA may require that a REMS "include such elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness." FDC Act § 505-1(f)(1). The elements to assure safe use of such a drug include, among other things, certain restricted distribution, procurement, and dispensing systems. For example, one element to assure safe use is that "the drug be dispensed to patients only in certain health care settings, such as hospitals." Id. § 505-1(f)(3)(C). Another is that "the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results." Id. § 505-1(f)(3)(D). Several drug products, including REVLIMID and THALOMID, are subject to an approved REMS incorporating elements to assure safe use restrictions that limit their availability, such that generic drug manufacturers cannot procure drug product sample through normal distribution channels.

In developing REMS, Congress directed FDA to, among other things, ensure that elements to assure safe use "not be unduly burdensome on patient access to the drug," FDC Act § 505-1(f)(2)(C), and, in an effort "to minimize the burden on the health care delivery system," id. § 505-1(f)(2)(D), design elements to assure safe use that are "compatible with established distribution, procurement, and dispensing systems . . . ." Id. § 505-1(f)(2)(D)(ii). In addition, FDA, through the Agency's Drug Safety and Risk Management Advisory Committee, must seek public input about how elements to assure safe use can be standardized "so as not to be – (i) unduly burdensome on patient access to the drug; and (ii) to the extent practicable, minimize the burden on the health care delivery system." Id. § 505-1(f)(5)(A). FDA must then, at least annually, evaluate and assess whether elements to assure safe use on one or more drugs meet these goals, and must issue or modify Agency guidelines – or modify elements to assure safe use – to meet such goals. See id. § 505-1(f)(5)(B)-(C).

Recognizing the potential that REMS restricted distribution programs could be used to block or delay generic competition, Congress included in FDAAA a provision amending the FDC Act mandating that REMS elements to assure safe use not be used as an obstacle to generic drug approval. Specifically, FDC Act § 505-1(f)(8) states:

> ***No holder of an approved covered application shall use any element to assure safe use*** required by [FDA] under [FDC Act § 505-1(f)] ***to block or delay approval of an application under section 505(b)(2) or (j)*** or to prevent application of such element under [FDC Act § 505-1(i)(1)(B)] to a drug that is the subject of an [ANDA].

FDC Act § 505-1(f)(8) (emphasis added).

FDAAA also amended the FDC Act to create new provisions for the enforcement of § 505-1. Specifically, under new FDC Act § 502(y), a drug is deemed to be misbranded "[i]f it is a drug subject to an approved [REMS] pursuant to section 505(p) and the responsible person (as such term is used in section 505-1) ***fails to comply with a requirement of such strategy provided for under subsection*** (d), (e), or ***(f) of section 505-1***." FDC Act § 502(y) (emphasis added). In addition, FDAAA amended the law to add new § 303(f)(4), which states that "[a]ny responsible person (as such term is used in section 505-1) ***that violates a requirement of section*** 505(o), 505(p), or ***505-1*** shall be subject to a civil monetary penalty" of up to $10 million for all violations adjudicated in a single proceeding. FDC Act § 303(f)(4)(A) (emphasis added).

With respect to the enforcement of these provisions for a product deemed to have an approved REMS in effect, FDAAA states that such a product "is subject to enforcement by [FDA] to the same extent as any other [REMS] under [FDC Act § 505-1], except that [FDC Act §§] 303(f)(4) and 502(y) . . . shall not apply to such strategy before [FDA] has completed review of, and acted on, the first assessment of such strategy under [FDC Act § 505-1]." FDAAA § 909(b)(2)(B).

FDA has not yet, to Dr. Reddy's knowledge, used its new statutory authority to take enforcement action against a responsible person for failing to comply with a REMS requirement under the FDC Act, either generally or specifically with respect to FDC Act § 505-1(f)(8).

### B. Delaying Generic Competition Through REMS Gaming

REMS requirements that restrict distribution, procurement, and dispensing of a drug product can be used to block or delay generic competition. Indeed, Dr. Reddy's recent attempts to procure a sufficient quantity of REVLIMID from Celgene for bioequivalence testing purposes is one recent case in which the company believes this occurred. Another recent example concerns Barr Laboratories, Inc.'s ("Barr's") attempts to procure drug product sample for another Celgene drug product – THALOMID.

In August 2008, Dr. Reddy's sent a letter to Celgene requesting that the company provide REVLIMID to Dr. Reddy's for bioequivalence study testing purposes. Dr. Reddy's agreed to reimburse Celgene for the fair market value of the requested REVLIMID drug product, as well as any shipping costs. In addition, Dr. Reddy's assured Celgene that Dr. Reddy's procedures for conducting any required testing

involving lenalidomide and the REVLIMID drug product provided by Celgene will fully comply with FDA requirements, and that Dr. Reddy's controls with respect to lenalidomide will be comparable to the RevAssist[SM] program. Dr. Reddy's requested a timely response to the company's request. Celgene did not respond.

Dr. Reddy's sent a second letter to Celgene in December 2008. In addition to repeating the company's request for biostudy drug sample and offering to pay Celgene the fair market value of the requested REVLIMID drug product, Dr. Reddy's reminded Celgene that FDC Act § 505-1(f)(8) prevents a company from using a REMS to block or delay generic competition, and that Celgene's failure to provide the requested sample quantity could result in Dr. Reddy's seeking a remedy from FDA and/or the FTC. Celgene finally responded to Dr. Reddy's letters in January 2009. Celgene's 1-page response dismisses Dr. Reddy's biostudy sample request in a single sentence: "Celgene has no obligation to supply Dr. Reddy's with REVLIMID and declines to do so." Letter from Maria E. Pasquale, Vice President and Chief Counsel, Celgene, to Jennifer K. Benneson, Vice President, Legal Affairs, Dr. Reddy's (Jan. 12, 2009) (Attachment #1).

Celgene's efforts to block generic competition with respect to REVLIMID appear to be part of a company-wide campaign to block generic competition for its drug products. Indeed, Celgene has taken similar types of actions with respect to THALOMID. In patent infringement litigation against Barr concerning Barr's submission of ANDA No. 78-505 (which is currently pending at FDA), Barr has asserted counterclaims that include tortious interference with a prospective business relationship and/or economic advantage, monopolization, attempted monopolization and conspiracy to monopolize, and conspiracy in restraint of trade. Barr's counterclaims revolve primarily around the allegation that Celgene unlawfully interfered with Barr's relationship with a third party supplier of thalidomide called Seratec. According to Barr:

> While negotiating with [Barr] to execute a thalidomide supply agreement, Seratec entered an exclusive supply arrangement with Celgene, whereby Seratec agreed to supply thalidomide [Active Pharmaceutical Ingredient ("API")] to Celgene alone and not to any other company. Seratec refused to supply [Barr] with thalidomide API or provide a [Drug Master File] reference letter on [Barr's] behalf because of the exclusive thalidomide API supply agreement Seratec executed with Celgene.

Barr Laboratories, Inc., Answer, Counterclaims and Demand for Jury Trial at 43, Celgene Corp. v. Barr Labs., Inc., CA No. 07-286 (D.N.J. Mar. 1, 2007) (Attachment #2). Barr alleges that "Celgene required Seratec to enter into an exclusive supply agreement with it

for the purpose of interfering with another company's ability to market a thalidomide product," id., and that Barr's ANDA was significantly delayed while the company searched for an alternative supply of drug product and conducted new bioequivalence studies. See id. at 43-44.

In turn, Celgene submitted a citizen petition to FDA requesting that the Agency not approve Barr's ANDA because, among other things, it raises unacceptable safety risks insofar as Celgene's S.T.E.P.S.® program is concerned, see Citizen Petition of Celgene, FDA Docket No. 2007-P-0113-0002, at 1-2 (Sept. 20, 2007). Celgene also alleged in its patent infringement litigation against Barr that Barr engaged in illegal or inequitable conduct by obtaining drug product necessary for Barr to conduct bioequivalence testing not in accordance with Celgene's S.T.E.P.S.® program. Specifically, Celgene alleges that:

> Barr, in an effort to obtain Thalomid® for use in its ANDA application, obtained 280 capsules of the 50mg, 140 capsules of the 100mg, and 924 capsules of the 200mg Thalomid® in violation of the product labels and S.T.E.P.S.® system by improperly purchasing the drug from a pharmacy. Upon information and belief, Barr did not attempt to obtain the drug in accordance with the FDA-mandated S.T.E.P.S.® system.

Reply to Counterclaims at 25, Celgene Corp. v. Barr Labs., Inc., CA No. 07-286 (D.N.J. Apr. 5, 2007) (Attachment #3).

In other words, a company can tie up the supply of a REMS restricted distribution drug product, thereby forcing a generic manufacturer to find alternative means of obtaining the RLD product – that Celgene, for example, has stated to Dr. Reddy's it "has no obligation to supply" – only to be faced with allegations that it unlawfully procured the drug product. Such efforts are nothing more than crude attempts to delay or block generic competition and clearly violate the REMS anti-gaming statutory provision at FDC Act § 505-1(f)(8).

Moreover, the use of REMS to prevent generic competition upsets the delicate balance between innovator intellectual property protection interests and timely generic entry into the market that Congress intended when it passed the Hatch-Waxman Amendments by permitting NDA holders to manipulate the REMS requirements to obtain a *de facto* and unwarranted period of market exclusivity.[4] The abuse of REMS as

---

[4] See, e.g., Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323, 1326 (Fed. Cir. 2001) ("These provisions of the Hatch-Waxman Amendments emerged from Congress' efforts

a lifecycle management tool to block or delay generic competition is in the same vein as other efforts (e.g., multiple 30-month stays and citizen petitions) some companies have used to extend marketing protections and that have upset the balance of the Hatch-Waxman Amendments. Those and other anti-competitive efforts, many of which the FTC has commented on and objected to, have been, to a large extent, remedied by subsequent amendments to the FDC Act. In the case of REMS gaming, however, Congress had the foresight to predict that REMS could be used to adversely affect generic competition and handed FDA the tools necessary to prevent REMS abuse.

### C. FDA Should Establish Procedures to Facilitate Generic Drug Approval and Enforce the FDC Act to Prevent REMS Gaming

While Dr. Reddy's agrees that certain restrictions are needed to assure the safe use of REVLIMID and THALOMID and other REMS drug products because of their inherent toxicity or potential harmfulness, such restrictions should not be used to prevent generic drug manufacturers from obtaining RLD sample for use in bioequivalence testing necessary to obtain ANDA (or 505(b)(2) application) approval. And companies that use REMS for anti-competitive purposes should not go unchecked. As discussed above, FDA has the authority to take enforcement action when a company games REMS to block or delay generic competition.

In an effort to more clearly describe FDA's regulatory procedures and enforcement procedures and practices with respect to innovator companies that seek to use REMS to block or delay generic competition, Dr. Reddy's requests that FDA issue a CPG or guidance document. Under procedures more fully described in a CPG or guidance document, a generic applicant could obtain a letter from FDA describing the Agency's findings that such generic applicant has agreed to applicable distribution restrictions necessary to assure safe use of the REMS restricted distribution drug product during bioequivalence testing. The generic applicant would provide a copy of that letter to an RLD sponsor with a request to purchase, at fair market value, a sufficient quantity of the REMS drug product for bioequivalence testing purposes. If the RLD sponsor fails to provide the generic applicant with the requested drug product in a timely manner (e.g., within 30 days of receiving a request) notwithstanding FDA's authorization to do so, then FDA should make clear in its CPG or guidance document that the Agency will consider such a failure to be a "use" of a REMS to block or delay generic competition in violation

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to balance two conflicting policy objectives: to induce name brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market.") (internal quote and citation omitted).

of FDC Act § 505-1(f)(8), and that enforcement action may be taken consistent with FDC Act §§ 502(y), and 303(f)(4).

Interestingly, Congress suggested a similar procedure in one draft of FDAAA that was passed by the U.S. House of Representatives. That bill – H.R. 2900 – included the following provisions:

> (5) LIMITATION – No holder of an approved application shall use any restriction on distribution required by the Secretary as necessary to assure safe use of the drug to block or delay approval of an application under section 505(b)(2) or (j) or to prevent application of such restriction under subsection (i)(1)(B) to a drug that is the subject of an abbreviated new drug application.
>
> (6) BIOEQUIVALENCE TESTING – Notwithstanding any other provisions in this subsection, the holder of an approved application that is subject to distribution restrictions required under this subsection that limit the ability of a sponsor seeking approval of an application under subsection 505(b)(2) or (j) to purchase on the open market a sufficient quantity of drug to conduct bioequivalence testing shall provide to such a sponsor a sufficient amount of drug to conduct bioequivalence testing if the sponsor seeking approval under section 505(b)(2) or (j) –
>
> > (A) agrees to such restrictions on distribution as the Secretary finds necessary to assure safe use of the drug during bioequivalence testing; and
> >
> > (B) pays the holder of the approved application the fair market value of the drug purchased for bioequivalence testing.
>
> (7) LETTER BY SECRETARY– Upon a showing by the sponsor seeking approval under section 505(b)(2) or (j) that the sponsor has agreed to such restrictions necessary to assure safe use of the drug during bioequivalence testing, the Secretary shall issue to the sponsor seeking to conduct bioequivalence testing a letter that describes the Secretary's finding which shall serve as proof that the sponsor has satisfied the requirements of subparagraph (6)(A).

H.R. 2900, 110th Cong. § 901 (2007) (as passed by the House of Representatives, July 16, 2007).

Although FDAAA included only section (5) above (i.e., FDC Act § 505-1(f)(8)), clearly Congress was concerned about the potential to game REMS to adversely affect generic competition and anticipated a need for FDA to develop procedures for generic companies to obtain bioequivalence testing supply.[5] FDA should do so now, and should take immediate enforcement action against a company that fails to provide biostudy drug product sample in light of FDA's authorization to do so.

Dr. Reddy's recognizes that FDAAA § 909(b)(2)(B) limits FDA's authority to take enforcement action with respect to a product under a "deemed REMS;" however, the law also states that such a product "is subject to enforcement by [FDA] ***to the same extent as any other [REMS] under [FDC Act § 505-1]***." FDAAA § 909(b)(2)(B) (emphasis added). As such, if FDA finds that a "deemed REMS" product sponsor has violated FDC Act § 505-1, then the Agency should take other appropriate enforcement action not specifically precluded by FDAAA § 909(b)(2)(B) to influence the sponsor's anti-competitive commercial activities. For example, FDA could issue a Warning Letter or Untitled Letter to the sponsor of a REMS product if that sponsor has delayed or blocked generic competition in violation of FDC Act § 505-1(f)(8), because, for example, such sponsor has failed to provide biostudy drug product sample in light of FDA's authorization to do so.

In addition to establishing procedures for generic applicants to obtain drug product sample for bioequivalence testing purposes, FDA should incorporate into the Agency's REMS with sponsors a provision stating that, consistent with FDC Act § 505-1(f)(8), the listed drug sponsor will not to use REMS elements to assure safe use that restrict product distribution to delay or block generic competition. A company that nevertheless uses a REMS to delay or block generic competition should be subject to immediate enforcement action. Incorporating such information into REMS would help ensure that FDA is meeting Congress' directive that elements to assure safe use "not be unduly burdensome on patient access to the drug," FDC Act § 505-1(f)(2)(C), and that such elements are "compatible with established distribution, procurement, and dispensing systems . . . ." Id. § 505-1(f)(2)(D)(ii).

---

[5] Dr. Reddy's understands that FDA's current policy is to follow similar procedures when a generic applicant requests the Agency's assistance in obtaining sample of a drug product under a restricted distribution program for bioequivalence testing purposes; however, that policy is not, to Dr. Reddy's knowledge, incorporated into any written and publicly available FDA procedures. Congress' decision not to include the procedures described in H.R. 2900 should not, therefore, be interpreted as a rejection of the actions Dr. Reddy's requests in this Citizen Petition.

Finally, because of the anti-competitive effects of REMS gaming, FDA should refer any complaint the Agency receives about alleged REMS gaming to the FTC. The FTC can then determine whether or not it is appropriate to take enforcement action under the laws and regulations the Commission enforces.

## III. ENVIRONMENTAL IMPACT

Pursuant to 21 C .F.R. § 25.31, an environmental impact statement is not required for this action because the grant of the Citizen Petition would not have an effect on the environment.

## IV. ECONOMIC IMPACT

Information on the economic impact of the action requested by this Citizen Petition will be submitted if requested by FDA.

## CERTIFICATION

Dr. Reddy's makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: January 2009. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: DRDr. Reddy's. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.[6]

---

[6] FDA has clarified that the citizen petition procedures at FDC Act § 505(q) apply to petitions that affect an ANDA or 505(b)(2) application that is pending at the time the citizen petition is submitted to FDA. See, FDA, Draft Guidance for Industry, Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act, at 4 (Jan. 2009). Dr. Reddy's does not – and cannot as a result

DR. REDDY'S

Respectfully submitted,

Kumar Sekar, Ph.D.
Senior Director
Regulatory Affairs and Compliance

cc: Gary J. Buehler
Director, Office of Generic Drugs, FDA
Elizabeth H. Dickinson, Esq.
Kim E. Dettelbach, Esq.
Office of Chief Counsel, FDA
Jon Liebowitz
Chairman, FTC

---

of Celgene's refusal to provide drug product so that Dr. Reddy's can conduct the required bioequivalence testing to submit an ANDA – have an ANDA pending at FDA for a generic version of REVLIMID or another drug product subject to a REMS restricted distribution requirement. Nevertheless, Dr. Reddy's is aware of at least one pending ANDA – Barr's ANDA No. 78-505 for a generic version of THALOMID – that serves as a basis for FDA to consider this Citizen Petition under § 505(q).

# EXHIBIT 3

Table of Contents

# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**Washington, D.C. 20549**

# FORM 10-K

(Mark one)

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the fiscal year ended December 31, 2009**

**or**

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the transition period from _____ to _____**

**Commission file number 0-16132**

# CELGENE CORPORATION

(Exact name of registrant as specified in its charter)

| **Delaware** | **22-2711928** |
|---|---|
| (State or other jurisdiction of incorporation or organization) | (I.R.S. Employer Identification No.) |
| **86 Morris Avenue Summit, New Jersey** | **07901** |
| (Address of principal executive offices) | (Zip Code) |

**(908) 673-9000**
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

| **Title of each class** | **Name of each exchange on which registered** |
|---|---|
| Common Stock, par value $.01 per share | NASDAQ Global Select Market |

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

Yes ☑ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act.

Yes ☐ No ☑

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes ☑ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

Yes ☑ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

| Large accelerated filer ☑ | Accelerated filer ☐ | Non-accelerated filer ☐ (Do not check if a smaller reporting company) | Smaller reporting company ☐ |
|---|---|---|---|

Indicate by check mark whether the registrant is a shell company (as defined in Rule12b-2 of the Act).

Yes ☐ No ☑

The aggregate market value of voting stock held by non-affiliates of the registrant on June 30, 2009, the last business day of the registrant's most recently completed second quarter was $21,935,672,339 based on the last reported sale price of the registrant's Common Stock on the NASDAQ Global Select Market on that date.

There were 459,730,918 shares of Common Stock outstanding as of February 11, 2010.

**Documents Incorporated by Reference**

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days of the end of the fiscal year ended December 31, 2009. The proxy statement is incorporated herein by reference into the following parts of the Form 10-K:

Part II, Item 5, Equity Compensation Plan Information

Part III, Item 10, Directors, Executive Officers and Corporate Governance;

Part III, Item 11, Executive Compensation;

Part III, Item 12, Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters;

Part III, Item 13, Certain Relationships and Related Transactions, and Director Independence;

Part III, Item 14, Principal Accountant Fees and Services.

**CELGENE CORPORATION**
**ANNUAL REPORT ON FORM 10-K**

**TABLE OF CONTENTS**


| Item No. | | Page |
|---|---|---|
| | Part I | |
| 1. | Business | 1 |
| 1A. | Risk Factors | 21 |
| 1B. | Unresolved Staff Comments | 34 |
| 2. | Properties | 34 |
| 3. | Legal Proceedings | 35 |
| 4. | Submission of Matters to a Vote of Security Holders | 39 |
| | Part II | |
| 5. | Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities | 40 |
| 6. | Selected Financial Data | 42 |
| 7. | Management's Discussion and Analysis of Financial Condition and Results of Operations | 43 |
| 7A. | Quantitative and Qualitative Disclosures About Market Risk | 65 |
| 8. | Financial Statements and Supplementary Data | 68 |
| 9. | Changes in and Disagreements With Accountants on Accounting and Financial Disclosure | 118 |
| 9A. | Controls and Procedures | 118 |
| 9B. | Other Information | 121 |
| | Part III | |
| 10. | Directors, Executive Officers and Corporate Governance | 121 |
| 11. | Executive Compensation | 121 |
| 12. | Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters | 121 |
| 13. | Certain Relationships and Related Transactions, and Director Independence | 121 |
| 14. | Principal Accountant Fees and Services | 121 |
| | Part IV | |
| 15. | Exhibits, Financial Statement Schedules | 122 |
| | Signatures and Power of Attorney | 128 |

Exhibit 3.2
Exhibit 21.1
Exhibit 23.1
Exhibit 31.1
Exhibit 31.2
Exhibit 32.1
Exhibit 32.2
EX-101 INSTANCE DOCUMENT
EX-101 SCHEMA DOCUMENT

EX-101 CALCULATION LINKBASE DOCUMENT
EX-101 LABELS LINKBASE DOCUMENT
EX-101 PRESENTATION LINKBASE DOCUMENT
EX-101 DEFINITION LINKBASE DOCUMENT

***If we are not able to effectively compete our business will be adversely affected.***

The pharmaceutical and biotech industry in which we operate is highly competitive and subject to rapid and significant technological change. Our present and potential competitors include major pharmaceutical and biotechnology companies, as well as specialty pharmaceutical firms, including, but not limited to:

- Takeda and Johnson & Johnson, compete with REVLIMID® and THALOMID®in the treatment of multiple myeloma and in clinical trials with our compounds;
- Eisai Co., Ltd., SuperGen, Inc. and Johnson & Johnson compete or may potentially compete with VIDAZA®;
- Amgen, which potentially competes with our TNF-α and kinase inhibitors;
- AstraZeneca plc, which potentially competes in clinical trials with our compounds and TNF-α inhibitors;
- Biogen Idec Inc. and Genzyme Corporation, both of which are generally developing drugs that address the oncology and immunology markets;
- Bristol Myers Squibb Co., which potentially competes in clinical trials with our compounds and TNF-α inhibitors;
- F. Hoffman-La Roche Ltd., which potentially competes in clinical trials with our IMiDs® compounds and TNF-α inhibitors;
- Johnson & Johnson, which potentially competes with certain of our proprietary programs, including our oral anti-inflammatory programs;
- Novartis, which potentially competes with our compounds and kinase programs; and
- Pfizer, which potentially competes in clinical trials with our kinase inhibitors.

Many of these companies have considerably greater financial, technical and marketing resources than we do. This enables them, among other things, to make greater research and development investments and spread their research and development costs, as well as their marketing and promotion costs, over a broader revenue base. Our competitors may also have more experience and expertise in obtaining marketing approvals from the FDA, and other regulatory authorities. We also experience competition from universities and other research institutions, and in some instances, we compete with others in acquiring technology from these sources. The pharmaceutical industry has undergone, and is expected to continue to undergo, rapid and significant technological change, and we expect competition to intensify as technical advances in the field are made and become more widely known. The development of products, including generics, or processes by our competitors with significant advantages over those that we are seeking to develop could cause the marketability of our products to stagnate or decline.

***We may be required to modify our business practices, pay fines and significant expenses or experience losses due to governmental investigations or other litigation.***

From time to time, we may be subject to governmental investigation or litigation on a variety of matters, including, without limitation, regulatory, intellectual property, product liability, antitrust, consumer, commercial, securities and employment litigation and claims and other legal proceedings that may arise from the conduct of our business as currently conducted or as conducted in the future.

In particular, we are subject to significant product liability risks as a result of the testing of our products in human clinical trials and for products that we sell after regulatory approval.

Pharmaceutical companies involved in Hatch-Waxman litigation are often subject to follow-on lawsuits and governmental investigations, which may be costly and could result in lower-priced generic products that are competitive with our products being introduced to the market.

In the fourth quarter of 2009, we received a civil inquiry and demand from the Federal Trade Commission (FTC). The FTC requested documents and other information relating to requests by generic companies to purchase our patented THALOMID® and REVLIMID®brand drugs in order to evaluate whether there is reason to believe that we have engaged in unfair methods of competition. We continue to cooperate with the FTC's request for information.

Litigation and governmental investigations are inherently unpredictable and may:

- result in rulings that are materially unfavorable to us, including a requirement that we pay significant damages, fines or penalties or prevent us from operating our business in a certain manner;
- cause us to change our business operations to avoid perceived risks associated with such litigation or investigations;
- have an adverse affect on our reputation and the demand for our products; and
- require the expenditure of significant time and resources, which may divert the attention of our management and interfere with the pursuit of our strategic objectives.

While we maintain insurance for certain risks, the amount of our insurance coverage may not be adequate to cover the total amount of all insured claims and liabilities. It also is not possible to obtain insurance to protect against all potential risks and liabilities. If any litigation or governmental investigation were to have a material adverse result, there could be a material impact on our results of operations, cash flows, or financial position. See also Legal Proceedings contained in Part I, Item 3 of this Annual Report on Form 10-K.

***The development of new biopharmaceutical products involves a lengthy and complex process, and we may be unable to commercialize any of the products we are currently developing.***

Many of our drug candidates are in the early or mid-stages of research and development and will require the commitment of substantial financial resources, extensive research, development, preclinical testing, clinical trials, manufacturing scale-up and regulatory approval prior to being ready for sale. This process involves a high degree of risk and takes many years. Our product development efforts with respect to a product candidate may fail for many reasons, including the failure of the product candidate in preclinical studies; adverse patient reactions to the product candidate or indications or other safety concerns; insufficient clinical trial data to support the effectiveness or superiority of the product candidate; our inability to manufacture sufficient quantities of the product candidate for development or commercialization activities in a timely and cost-efficient manner; our failure to obtain, or delays in obtaining, the required regulatory approvals for the product candidate, the facilities or the process used to manufacture the product candidate; or changes in the regulatory environment, including pricing and reimbursement, that make development of a new product or of an existing product for a new indication no longer desirable. Moreover, our commercially available products may require additional studies with respect to approved indications as well as new indications pending approval.

The stem cell products that we are developing through our CCT subsidiary may represent substantial departures from established treatment methods and will compete with a number of traditional products and therapies which are now, or may be in the future, manufactured and marketed by major pharmaceutical and biopharmaceutical companies. Furthermore, public attitudes may be influenced by claims that stem cell therapy is unsafe, and stem cell therapy may not gain the acceptance of the public or the medical community.

**SIGNATURES AND POWER OF ATTORNEY**

KNOW ALL MEN BY THESE PRESENTS, that each person or entity whose signature appears below constitutes and appoints Sol J. Barer and Robert J. Hugin, and each of them, its true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for it and in its name, place and stead, in any and all capacities, to sign any and all amendments to this Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done, as fully to all contents and purposes as it might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of Section 13 or 15 (d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

**CELGENE CORPORATION**

By: /s/ Sol J. Barer
Sol J. Barer
Chairman of the Board and
Chief Executive Officer

Date: February 18, 2010

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

| Signature | Title | Date |
|---|---|---|
| /s/ Sol J. Barer<br>Sol J. Barer | Chairman of the Board and Chief Executive Officer | February 18, 2010 |
| /s/ Robert J. Hugin<br>Robert J. Hugin | Director, Chief Operating Officer | February 18, 2010 |
| /s/ David W. Gryska<br>David W. Gryska | Chief Financial Officer | February 18, 2010 |
| /s/ Michael D. Casey<br>Michael D. Casey | Director | February 18, 2010 |
| /s/ Carrie S. Cox<br>Carrie S. Cox | Director | February 18, 2010 |
| /s/ Rodman L. Drake<br>Rodman L. Drake | Director | February 18, 2010 |

# EXHIBIT 4

Table of Contents

# UNITED STATES SECURITIES AND EXCHANGE COMMISSION

**Washington, D.C. 20549**

# Form 10-K

(Mark one)

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the fiscal year ended December 31, 2010**

**or**

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the transition period from to**

**Commission file number 001-34912**

# CELGENE CORPORATION

*(Exact name of registrant as specified in its charter)*

| **Delaware** | **22-2711928** |
|---|---|
| *(State or other jurisdiction of incorporation or organization)* | *(I.R.S. Employer Identification No.)* |
| **86 Morris Avenue**<br>**Summit, New Jersey**<br>*(Address of principal executive offices)* | **07901**<br>*(Zip Code)* |

**(908) 673-9000**
*(Registrant's telephone number, including area code)*

**Securities registered pursuant to Section 12(b) of the Act:**

| Title of Each Class | Name of Each Exchange on Which Registered |
|---|---|
| Common Stock, par value $.01 per share | NASDAQ Global Select Market |
| Contingent Value Rights | NASDAQ Global Select Market |

**Securities registered pursuant to Section 12(g) of the Act:**
**None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☑ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☑ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

| Large accelerated filer ☑ | Accelerated filer ☐ | Non-accelerated filer ☐ (Do not check if a smaller reporting company) | Smaller reporting company ☐ |
|---|---|---|---|

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☑

The aggregate market value of voting stock held by non-affiliates of the registrant on June 30, 2010, the last business day of the registrant's most recently completed second quarter, was $23,349,073,366 based on the last reported sale price of the registrant's Common Stock on the NASDAQ Global Select Market on that date.

There were 464,898,965 shares of Common Stock outstanding as of February 18, 2011.

**Documents Incorporated by Reference**

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days of the end of the fiscal year ended December 31, 2010. The proxy statement is incorporated herein by reference into the following parts of the Form 10-K:

Part II, Item 5, Equity Compensation Plan Information

Part III, Item 10, Directors, Executive Officers and Corporate Governance;

Part III, Item 11, Executive Compensation;

Part III, Item 12, Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters;

Part III, Item 13, Certain Relationships and Related Transactions, and Director Independence;

Part III, Item 14, Principal Accountant Fees and Services.

**CELGENE CORPORATION**

**ANNUAL REPORT ON FORM 10-K**

**TABLE OF CONTENTS**


| Item No. | | Page |
|---|---|---|
| | **Part I** | |
| 1. | Business | 1 |
| 1A. | Risk Factors | 21 |
| 1B. | Unresolved Staff Comments | 34 |
| 2. | Properties | 35 |
| 3. | Legal Proceedings | 35 |
| 4. | Submission of Matters to a Vote of Security Holders | 37 |
| | **Part II** | |
| 5. | Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities | 38 |
| 6. | Selected Financial Data | 40 |
| 7. | Management's Discussion and Analysis of Financial Condition and Results of Operations | 42 |
| 7A. | Quantitative and Qualitative Disclosures About Market Risk | 60 |
| 8. | Financial Statements and Supplementary Data | 63 |
| 9. | Changes in and Disagreements With Accountants on Accounting and Financial Disclosure | 117 |
| 9A. | Controls and Procedures | 117 |
| 9B. | Other Information | 120 |
| | **Part III** | |
| 10. | Directors, Executive Officers and Corporate Governance | 120 |
| 11. | Executive Compensation | 120 |
| 12. | Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters | 120 |
| 13. | Certain Relationships and Related Transactions, and Director Independence | 120 |
| 14. | Principal Accountant Fees and Services | 120 |
| | **Part IV** | |
| 15. | Exhibits, Financial Statement Schedules | 120 |
| | Signatures and Power of Attorney | 126 |

EX-21.1
EX-23.1
EX-31.1
EX-31.2
EX-32.1
EX-32.2
EX-101 INSTANCE DOCUMENT
EX-101 SCHEMA DOCUMENT
EX-101 CALCULATION LINKBASE DOCUMENT
EX-101 LABELS LINKBASE DOCUMENT
EX-101 PRESENTATION LINKBASE DOCUMENT
EX-101 DEFINITION LINKBASE DOCUMENT

We have received a Paragraph IV Certification Letter dated August 30, 2010, advising us that Natco Pharma Limited of Hyderabad, India, or Natco, submitted an ANDA to the FDA. See Part 1, Item 3, "Legal Proceedings — Revlimid®" of this report for further discussion.

***If we are not able to effectively compete our business will be adversely affected.***

The pharmaceutical and biotech industry in which we operate is highly competitive and subject to rapid and significant technological change. Our present and potential competitors include major pharmaceutical and biotechnology companies, as well as specialty pharmaceutical firms, including, but not limited to:

- Takeda and Johnson & Johnson, which compete with REVLIMID® and THALOMID® in the treatment of multiple myeloma and in clinical trials with our compounds;
- Eisai Co., Ltd., SuperGen, Inc. and Johnson & Johnson, which compete or may potentially compete with VIDAZA®, in addition Eisai Co., Ltd. potentially competes with ABRAXANE®, and in other oncology products in general;
- Amgen, which potentially competes with our TNF-α and kinase inhibitors;
- AstraZeneca plc, which potentially competes in clinical trials with our compounds and TNF-α inhibitors;
- Biogen Idec Inc. and Genzyme Corporation, both of which are generally developing drugs that address the oncology and immunology markets;
- Bristol Myers Squibb Co., which potentially competes with ABRAXANE®, and in clinical trials with our compounds and TNF-α inhibitors, in addition to other oncology products in general;
- F. Hoffman-La Roche Ltd., which potentially competes in clinical trials with our IMiDs® compounds and TNF-α inhibitors, in addition to other oncology products in general;
- Johnson & Johnson, which potentially competes with certain of our proprietary programs, including our oral anti-inflammatory programs;
- Abbott Laboratories, which potentially competes with our oral anti-inflammatory programs;
- Novartis, which potentially competes with our compounds and kinase programs;
- Pfizer, which potentially competes in clinical trials with our kinase inhibitors; and
- Sanofi-Aventis, which competes with ABRAXANE®, in addition to other oncology products in general.

Many of these companies have considerably greater financial, technical and marketing resources than we do. This enables them, among other things, to make greater research and development investments and spread their research and development costs, as well as their marketing and promotion costs, over a broader revenue base. Our competitors may also have more experience and expertise in obtaining marketing approvals from the FDA, and other regulatory authorities. We also experience competition from universities and other research institutions, and in some instances, we compete with others in acquiring technology from these sources. The pharmaceutical industry has undergone, and is expected to continue to undergo, rapid and significant technological change, and we expect competition to intensify as technical advances in the field are made and become more widely known. The development of products, including generics, or processes by our competitors with significant advantages over those that we are seeking to develop could cause the marketability of our products to stagnate or decline.

***We may be required to modify our business practices, pay fines and significant expenses or experience losses due to litigation or governmental investigations.***

From time to time, we may be subject to litigation or governmental investigation on a variety of matters, including, without limitation, regulatory, intellectual property, product liability, antitrust, consumer, whistleblower, commercial, securities and employment litigation and claims and other legal proceedings that may arise from the conduct of our business as currently conducted or as conducted in the future.

In particular, we are subject to significant product liability risks as a result of the testing of our products in human clinical trials and for products that we sell after regulatory approval.

Pharmaceutical companies involved in Hatch-Waxman litigation are often subject to follow-on lawsuits and governmental investigations, which may be costly and could result in lower-priced generic products that are competitive with our products being introduced to the market.

In the fourth quarter of 2009, we received a Civil Investigative Demand (CID) from the U.S. Federal Trade Commission, or the FTC. The FTC requested documents and other information relating to requests by generic companies to purchase our patented REVLIMID® and THALOMID® brand drugs in order to evaluate whether there is reason to believe that we have engaged in unfair methods of competition. In the first quarter of 2010, the State of Connecticut referenced the same issues as those referenced in the 2009 CID and issued a subpoena. In the fourth quarter of 2010, we received a second CID from the FTC relating to this matter. We continue to respond to requests for information.

In the first quarter of 2011, we received a letter from the United States Attorney for the Central District of California informing us that we were under investigation relating to our promotion of the drugs THALOMID® and REVLIMID® regarding off-label marketing and improper payments to physicians. We are cooperating with the Unites States Attorney in connection with this investigation.

On January 20, 2011, the Supreme Court of Canada ruled that the jurisdiction of the Patented Medicine Prices Review Board, or the PMPRB, extends to sales of drugs to Canadian patients even if the locus of sale is within the United States. This means that our U.S. sales of THALOMID® brand drug to Canadian patients under the special access program are subject to PMPRB jurisdiction from and after January 12, 1995. In accordance with the ruling of the Supreme Court of Canada, we have provided to-date data regarding these special access program sales to the PMPRB. In light of the approval of THALOMID® brand drug for multiple myeloma by Health Canada on August 4, 2010, this drug is now sold through our Canadian entity and is no longer sold to Canadian patients in the United States. The PMPRB's proposed pricing arrangement has not been determined. Depending on the calculation, we may be requested to return certain revenues associated with these sales and to pay fines. Should this occur, we would have to consider various legal options to address whether the pricing determination was reasonable.

Litigation and governmental investigations are inherently unpredictable and may:

- result in rulings that are materially unfavorable to us, including claims for significant damages, fines or penalties, and administrative remedies, such as exclusion and/or debarment from government programs, or other rulings that prevent us from operating our business in a certain manner;
- cause us to change our business operations to avoid perceived risks associated with such litigation or investigations;
- have an adverse affect on our reputation and the demand for our products; and
- require the expenditure of significant time and resources, which may divert the attention of our management and interfere with the pursuit of our strategic objectives.

While we maintain insurance for certain risks, the amount of our insurance coverage may not be adequate to cover the total amount of all insured claims and liabilities. It also is not possible to obtain insurance to protect against all potential risks and liabilities. If any litigation or governmental investigation were to have a material adverse result, there could be a material impact on our results of operations, cash flows or financial position. See also Legal Proceedings contained in Part I, Item 3 of this Annual Report on Form 10-K.

***The development of new biopharmaceutical products involves a lengthy and complex process, and we may be unable to commercialize any of the products we are currently developing.***

Many of our drug candidates are in the early or mid-stages of research and development and will require the commitment of substantial financial resources, extensive research, development, preclinical testing, clinical trials, manufacturing scale-up and regulatory approval prior to being ready for sale. This process involves a high degree of risk and takes many years. Our product development efforts with respect to a product candidate may fail for many

**SIGNATURES AND POWER OF ATTORNEY**

KNOW ALL MEN BY THESE PRESENTS, that each person or entity whose signature appears below constitutes and appoints Robert J. Hugin its true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for it and in its name, place and stead, in any and all capacities, to sign any and all amendments to this Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done, as fully to all contents and purposes as it might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of Section 13 or 15 (d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

**CELGENE CORPORATION**

By: /s/ Robert J. Hugin
Robert J. Hugin
Chief Executive Officer

Date: February 28, 2011

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

| Signature | Title | Date |
|---|---|---|
| /s/ Sol J. Barer<br>Sol J. Barer | Chairman of the Board | February 28, 2011 |
| /s/ Robert J. Hugin<br>Robert J. Hugin | Director, Chief Executive Officer | February 28, 2011 |
| /s/ Jacqualyn A. Fouse<br>Jacqualyn A. Fouse | Chief Financial Officer | February 28, 2011 |
| /s/ Michael D. Casey<br>Michael D. Casey | Director | February 28, 2011 |
| /s/ Carrie S. Cox<br>Carrie S. Cox | Director | February 28, 2011 |
| /s/ Rodman L. Drake<br>Rodman L. Drake | Director | February 28, 2011 |
| Michael A. Friedman<br>Michael A. Friedman | Director | February 28, 2011 |
| /s/ Gilla Kaplan<br>Gilla Kaplan | Director | February 28, 2011 |